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LETTERS TO THE EDITOR

Patients With High-Risk Acute Myocardial Infarction Randomized to One of Two Treatment Strategies: Delay and Eligibility Questions

Grines et al. (1) reported randomization of patients with high-risk acute myocardial infarction (AMI) to one of two treatment strategies, namely transfer for primary percutaneous transluminal coronary angioplasty (PTCA) or on-site thrombolysis. Randomization required a mean of 44 min (median 32 min) and resulted in a mean delay of 63 min (median 51 min) from emergency room arrival to delivery of thrombolytic treatment. The time from symptom onset to emergency room arrival was not presented. This time interval is important for judging the impact of the reported treatment delay on mortality (2).

In addition, it would be interesting to know the proportion of patients eligible for the study, that is, the numbers of AMI patients screened, number of patients matching high-risk criteria, and number of those excluded.

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Safety and Benefits of Transferring Patients With Acute Myocardial Infarction to Interventional Center for Immediate Angioplasty

The study by Grines et al. (1), which appeared recently in *JACC,* evaluated the safety and benefits of transfer of a high-risk patient suffering an acute myocardial infarction (AMI) to a regional interventional center for immediate angioplasty. The investigators concluded: "This trial demonstrated that patients with high-risk AMI at hospitals without percutaneous transluminal coronary angioplasty (PTCA) capabilities might have an improved outcome if transferred for emergency PTCA rather than being treated with thrombolytic therapy." In the editorial (2) that accompanied the study, Cannon and Baim stated "it appears that there may be benefit in prompt and efficient transfer of patients from a community hospital that does not offer primary percutaneous coronary intervention (PCI) to a nearby one that does." This begs an important question concerning the safety of transferring a patient with AMI. The investigators note that their study is underpowered to answer the question. The difficulty in recruitment of subjects and premature closure of the study suggest that the study group is a highly selective set of patients. Before the availability of immediate angioplasty it was believed that transfer was inappropriate for the AMI patient. This patient is at the greatest danger for extension of the infarction, serious arrhythmia, and congestive heart failure in the first hours after the infarction. Monitoring for and managing these complications are very difficult when the patient is transferring from one hospital to another.

Cannon and Baim (2) noted that success for PCI is related to the skill and experience of the interventionalist. Many hospitals with catherization laboratories have the availability of high-volume interventionalists. However, the majority of these physicians are unwilling to perform interventions at hospitals that do not routinely perform angioplasty. Because it is not a routine procedure, PTCA performed under emergency circumstances would represent a higher risk for the patient. As a solution to this problem, Cannon and Baim suggested a network of cardiac centers offering PCI around the clock.

Could immediate angioplasty be safely and effectively applied at the initial hospital? I believe that it is safer to bring the intervention to the patient rather than the patient to the interventionalist. For most patients with an AMI, this could be accomplished by expanding PTCA to any hospital with a catheterization laboratory. The use of routine PTCA at hospitals without back-up cardiovascular surgery would significantly extend PCI to the at-risk population and increase the availability of skilled interventionalists to provide the service.

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REPLY

In response to correspondents Pechlaner and Bellmann, the time from symptom onset to emergency room arrival was 140 ± 46 min in the transfer arm and 158 ± 162 min in the lytic arm ($p = 0.40$). Unfortunately, screening logs were not maintained, and we were

Table 1. Pooled Outcomes From Five Studies of Transfer for Primary PTCA Versus On Site: Lytics

	PCI	Lytic	p Value	Odds Ratio	95% CI
Death	103/1,468 (7.0%)	129/1,443 (8.9 %)	0.055	1.3	0.99–1.70
Nonfatal reMI	19/1,037 (1.8%)	68/1,022 (6.7 %)	< 0.0001	3.82	2.28–6.40
Total stroke	11/1,037 (1.1%)	22/1,022 (2.2 %)	0.049	2.05	0.99–4.25
Death/stroke/MI	121/1,468 (8.2%)	217/1,443 (15.0%)	< 0.0001	1.97	1.56–2.49

CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention.

unable to determine the proportion of AMI acute myocardial infarction (AMI) patients eligible for enrollment in the study.

Dr. Silverman questioned the safety of transfer of the AMI patient. Although his concerns are valid, all emergency medical systems that would be transferring AMI patients are trained in advanced cardiac life support. These systems should be able to resuscitate AMI patients, as well as the staff in the emergency department or intensive care units of small hospitals.

In fact, five randomized trials of transfer for primary angioplasty have shown that transfer is safe and is associated with better outcomes compared to on site thrombolytics (1–5) (Table 1).

Experienced angioplasty operators may safely perform primary angioplasty in diagnostic catheterization laboratories. However, the expense of training staff, both in the laboratory and in recovery units, in addition to stocking expensive angioplasty equipment, may not be feasible in small hospitals.

Finally, it would be far easier to instruct emergency medical staff drivers to head in the correct direction—toward a primary angioplasty facility.

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Possible Risks to Patients Receiving Statins Combined With Other Medications

The American College of Cardiology/American Heart Association/National Heart Lung, and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory on Statins (1) was a timely review of an important issue, but I believe that additional information on the issue of drug interactions would be helpful to clinicians who manage patients receiving statins with other medications.

First, as for combining statins with CYP3A4 inhibitors, only lovastatin and simvastatin undergo extensive (90% or more) presystemic metabolism by CYP3A4 in the gut wall and liver (2). Hence, the risk of statin-induced myopathy due to CYP3A4 inhibitors appears to be considerably greater for lovastatin and simvastatin compared to the other statins. For example, potent CYP3A4 inhibitors such as itraconazole can produce 10- to 20-fold increases in the serum concentrations of lovastatin or simvastatin (3,4). Atorvastatin is also metabolized by CYP3A4, but it does not undergo as extensive presystemic metabolism as lovastatin and simvastatin. Accordingly, potent CYP3A4 inhibitors tend to produce two- to four-fold increases in atorvastatin serum concentrations (5,6). Pravastatin is not metabolized by CYP3A4 or other cytochrome P450 isozymes, and inhibition of CYP3A4 has little effect on its pharmacokinetics (4,6). Fluvastatin is metabolized primarily by CYP2C9 and also is unlikely to interact with CYP3A4 inhibitors (2).

Second, as for macrolides and statins, erythromycin and clarithromycin are correctly listed as potentially increasing the risk of statin-associated myopathy. As described above, this caution results from the ability of these two macrolide antibiotics to inhibit the CYP3A4 metabolism of lovastatin, simvastatin, and to a lesser extent atorvastatin (7,8). But a separate bullet point lists "Macrolide antibiotics" (page 571 under "Prevention" heading). This might lead some readers to conclude that azithromycin and dirithromycin interact with statins, but substantial evidence suggests that these macrolides do not inhibit CYP3A4 (9).

Finally, as for the interaction of calcium-channel blockers and statins, verapamil—a known CYP3A4 inhibitor—is listed as increasing the risk of statin-associated myopathy, but diltiazem is not mentioned. Available evidence suggests that verapamil and diltiazem are roughly equivalent (moderate) inhibitors of CYP3A4. Indeed, diltiazem has been shown in pharmacokinetic studies to increase serum concentrations of both lovastatin and simvastatin (10,11), and isolated cases of myopathy have been reported in patients receiving simvastatin plus diltiazem (12,13).